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MINIREVIEWS

COVID-19 and the liver: Are footprints still there?

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Abstract

The coronavirus disease 2019 (COVID-19) hit the entire world as a global pandemic and soon became the most important concern for all patients with chronic diseases. An early trend in higher mortality in patients with acute respiratory distress attracted all researchers to closely monitor patients for the involvement of other systems. It soon became apparent that patients with chronic liver diseases are at increased risk of mortality given their cirrhosis-associated immune dysfunction. Additionally, liver function abnormalities were noted in patients with severe COVID-19. Profound cytokine storm, direct viral infection, drugs and reactivation of viral infections were causes of deranged liver functions. Here, we discuss the relation between COVID-19 and chronic liver disease, specifically cirrhosis, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease (NAFLD), as well as the liver manifestations of COVID-19. The metabolic syndrome, obesity, diabetes mellitus and NAFLD were found to worsen outcome in different studies reported worldwide. Decompensated cirrhosis should be considered a risk factor for death and severe COVID-19. Recently, COVID-19 related cholangiopathy has also been reported with changes of secondary sclerosing cholangitis. The long-term persistence of viral antigens in gut epithelia raises concern regarding the future risk of autoimmune liver diseases.

Key Words: COVID-19; Chronic liver disease; Cirrhosis; Liver injury; Transaminases; Non-alcoholic fatty liver disease; Post-acute COVID-19 syndrome

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Core Tip: Coronavirus disease 2019 (COVID-19) and liver involvement have been a major concern since the beginning of the COVID-19 pandemic. Deranged liver functions with raised transaminases were reported in patients with severe COVID-19. On the other hand, acute hepatitis or liver failure was uncommon. Severe acute respiratory syndrome coronavirus 2 virus associated cytokine surge, systemic inflammation, direct viral infection, drugs such as remdesivir, steroids, and lopinavir-ritonavir were the main causative factor in raised transaminases. Patients with pre-existing chronic liver diseases especially non-alcoholic fatty liver disease were found to be risk factors for increased mortality in patients with severe COVID-19.

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INTRODUCTION

In December 2019, severe acute respiratory syndrome (SARS) caused by SARS- coronavirus 2 (SARS-CoV2), which belongs to the Coronaviridae family, was first detected in Wuhan, China. It soon spread to the rest of the world, and was declared a global pandemic in March 2020. In mild cases, the symptoms included fever, cough, body aches, malaise, loss of taste and smell. Approximately 15% of patients would eventually have respiratory compromise, hypoxia, and the need for invasive mechanical ventilation. Finally, multi-organ failure, coagulopathy, disseminated intravascular coagulation, acute respiratory distress syndrome, and hypoxia would follow. Over a period of more than 2 years, multiple waves of coronavirus disease 2019 (COVID-19) were observed in different geographical regions. As the virus mutated, there were many shifts in the clinical presentation. New symptoms of predominantly the upper respiratory tract such as sneezing and rhinitis, gastrointestinal symptoms such as diarrhea and non-specific abdominal pain, cardiac symptoms such as arrhythmias, ocular and neurological symptoms were reported. Additionally, as patients underwent more investigations, dysregulated coagulation and thrombosis were documented. Overall, liver involvement such as elevated liver enzymes ranged from 14% to 53% of patients in various studies. However, acute hepatitis or liver failure was uncommon. Furthermore, different studies worldwide have shown that non-alcoholic fatty liver disease (NAFLD), diabetes, hypertension, and obesity are significant risk factors for severe COVID-19.

A lockdown and a ban on air travel during the COVID-19 pandemic helped keep people with chronic illnesses at home. Their overall exposure to COVID-19 and other pathogens was constrained. Mild COVID-19 patients were isolated and quarantined in accordance with protocol and did not frequently undergo examinations. Patients with serious illnesses, however, were the only ones who underwent in-depth examinations. As a result, the majority of research mainly included individuals with serious diseases.

METHODS

We searched PubMed, Google Scholar, and Google from January 2020 to August 2022, for articles written in English that describe the liver effects of COVID-19, using the search terms “coronaviruses and liver”, “COVID-19 and liver”, “COVID-19 and liver symptoms”, “COVID-19 and hepatic”, “COVID-19 and liver function test”, “COVID-19 and liver inflammation”, “SARS-CoV-2 and liver”, “COVID-19 and NAFLD”, “COVID-19 and non-alcoholic fatty liver disease”, “COVID-19 and non-alcoholic fatty liver disease”, “COVID-19 and hepatitis”, and “COVID-19 and Vaccine”. Reference lists of the articles were scanned to identify any additional studies. The title and abstract of each article were read for the initial selection and then the full-text articles were read on availability. Reference lists of the full-text articles were scanned to identify any additional studies. All types of research articles, including original research articles, reviews, case series, short communications, and case reports were considered. Of the 667 articles identified, 313 were studied for this review.

SARS-COV2 HEPATOTROPISM

Due to a lack of significant laboratory testing and tissue biopsies from patients who were actively infected with SARS-CoV2, the mechanism of its replication is still not entirely understood.

SARS-CoV2 is an enveloped positive sense single stranded RNA virus with almost 80% identity with SARS-CoV. It has 4 structural proteins namely nucleocapsid, spike (S), membrane and enveloped proteins. The spike protein has multiple protrusions from the cell surface giving the virus its appearance and name. The angiotensin-converting enzyme 2 (ACE2) receptors are the potential site of entry for SARS-CoV2. ACE2 receptors are abundantly present on alveolar epithelium, lung, nasal epithelium etc. They are also present in fewer numbers in intestinal epithelium and liver[1]. The spike protein having two subunits S1 and S2 interacts with the ACE2 receptor for virus entry. However, ACE2 receptors are not sufficient alone and transmembrane serine proteases 2 (TMPRSS2) in addition to basic amino acid cleaving enzymes (FURIN) are essential for virus entry. According to single cell RNA sequencing analysis, hepatocytes have less co-expression of TMPRSS2 and ACE2 receptors. In the liver, cholangiocytes and sinusoidal endothelial cells have the highest expression of the ACE2 gene in almost 60% of the cell population as compared to hepatocytes (3% cells)[2,3]. Thus, a tissue or organoid model is required to understand the permissibility of liver cell types to SARS CoV-2 infection. Zhao *et al*[4] created human liver ductal organoids that were able to replicate SARS-CoV2 infection and expressed ACE2 and TMPRSS2. This suggests that the bile duct epithelium may be able to support pseudoparticle invasion. Despite a higher number of SARS-CoV2 virus receptors and a higher risk of infection of bile duct epithelia, COVID-19 does not follow a cholestatic pattern[5].

Studies conducted before the COVID-19 pandemic indicated that patients with hepatitis C virus (HCV)-related cirrhosis had 30 times higher ACE2 receptor expression on hepatocytes than healthy individuals[6]. The overexpression of ACE2 and TMPRSS2 has also been documented in obesity and nonalcoholic steatohepatitis patients, but not in patients with steatosis alone[7]. ACE2 is an interferon-inducible gene found in human respiratory epithelia, possibly SARS-CoV2 hepatotropism can be potentiated by the effects of systemic inflammation on hepatocytes and can lead to hepatocyte injury[8,9].

Additionally, ACE2 receptors are found in intestinal epithelia/enterocytes and SARS-CoV2 RNA has been documented by polymerase chain reaction in stool up to one week after recovery from respiratory illness. The latest data suggests that viral protein and RNA are found in intestinal biopsies for several months after resolution of respiratory illness[5,10].

In a study from Italy, postmortem wedged liver biopsy samples from 48 patients dying from severe COVID-19 were examined[11]. The results revealed vascular abnormalities such as sinusoidal and partial to complete portal venous microthromboses in almost 100% of samples. Additionally, mild portal inflammation, portal fibrosis, microvesicular and macrovesicular steatosis were documented in 66%, 60%, and 50% of patients, respectively. The latter finding is probably related to pre-existing liver disease such as NAFLD, as suggested by the presence of metabolic risk factors which were more prevalent in this patient group. Electron microscopy of these biopsies also revealed potential coronavirus-like particles, mitochondrial edema, and apoptosis of hepatocytes. However, comprehensive proteomic analysis of autopsy tissue from 19 patients with COVID-19 did not find signs of viral replication[12].

Furthermore, proteomic profiling revealed disrupted oxidative phosphorylation, fatty acid oxidation, and up-regulated immunological activators and profibrotic pathways. It is possible that hepatic steatosis, coagulative necrosis, and multi-organ dysfunction were all linked to mitochondrial dysfunction, dysregulated oxidative phosphorylation, etc[13].

LIVER FUNCTION TEST AND COVID-19

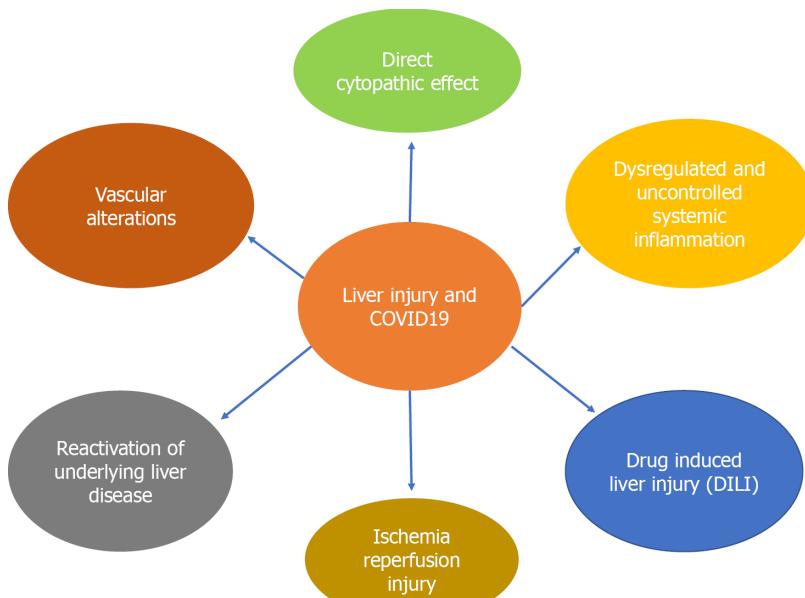
Despite higher SARS-CoV2 receptor expression on cholangiocytes and SECs, liver function derangement is usually in the form of a mild elevation in liver enzymes [1-2 upper limit of normal (ULN)][14-16].

Singh *et al*[17] showed that the presence of pre-existing liver illness has no effect on the incidence of liver enzyme elevations, although patients with pre-existing liver disease had a higher mortality rate.

In COVID-19, SARS-CoV2 induces a systemic inflammatory response and the release of cytokines. The predominant molecules are interleukin-6 and tumor necrosis factor alpha (TNF-alpha). Elevated cytokines result in hepatocyte inflammation and injury with liver ischemia, hypoxia, worsening of already existing chronic liver disease (CLD) and/or toxicity of medications used to treat the illness (Figure 1). Hepatic congestion as well as potential direct infection of hepatocytes although uncommon may also result in the release of transaminases[18].

However, indicators of muscle breakdown or systemic inflammation did not correlate with serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in hospitalised COVID-19 patients[19,20].

As AST level was frequently observed to surpass ALT level throughout the course of COVID-19, this was similar to patients with alcoholic liver disease, ischemic hepatitis and cirrhosis compared to a traditional hepatocellular pattern where ALT level is greater than AST[19]. Possibly, COVID-19 related mitochondrial dysfunction results in hepatic steatosis and altered hepatic perfusion is the result of sinusoidal microthrombosis[11,21-23].



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Figure 1 Effects of COVID-19 and liver injury interaction. COVID-19: Coronavirus disease 2019; DILI: Drug induced liver injury.

Respiratory epithelia involvement by SARS-CoV2 leads to defective oxygenation and the release of cytokines causes peripheral vasodilation and reduced tissue perfusion; the resultant perfusion and oxygenation defect causes systemic hypoxia which is a contributory factor in hepatocyte injury[24].

Early in the pandemic as no definitive treatment was available, experimental therapies in the form of drugs such as tocilizumab, remdesivir and lopinavir-ritonavir were used, which are known to cause hepatic injury[25-29]. Remdesivir was documented to cause elevations in liver enzymes in different studies[30,31]. Tocilizumab was well known for its risk of hepatitis B virus (HBV) reactivation and screening of hepatitis B and hepatitis C was advised before its use.

Ponziani *et al*[32] and Yip *et al*[33] showed that elevations in liver enzymes were associated with an increased incidence of shock, ICU admissions and invasive ventilation. However, these studies could be biased as hospitalized patients with severe disease undergo intensive monitoring of liver function (which increases the chances of detecting liver injury) as compared to home isolated patients with mild disease due to quarantine.

Some studies have suggested that there is no apparent correlation between liver function derangement and mortality[34,35]. Others have suggested an increased risk of death in patients with ALT levels > ULN[16,36,37].

According to Bangash *et al*[38], elevated liver transaminases linked to COVID-19 are more likely caused by severity of the disease, in which the host's reaction and iatrogenic factors such as medication and invasive ventilation cause bystander liver injury and thus explain its link to mortality in a manner similar to that of sepsis[38]. Because of this, clinicians must focus more on these factors than just elevated aminotransferases especially in patients with no pre-existing liver disease.

COVID-19 AND CLD

In the early days of the COVID-19 pandemic, the hepatology community worked fast to establish the risk of SARS-CoV2 acquisition and harmful COVID-19 outcome in pre-existing CLD. According to data from major case series and population-level electronic health records during the first global spike, patients with CLD were not overrepresented, indicating that these diseases did not make patients more susceptible to infection[15,39]. In fact, a significant North American study discovered that people with cirrhosis had a decreased probability of SARS-CoV2 positivity, probably due to improved awareness, testing, and patient adherence to public health recommendations for home isolation and quarantine. However, it is now evident that individuals with cirrhosis are more likely to experience negative COVID-19 outcomes after infection, including mortality. Multiple lines of evidence, such as findings from the international registries SECURE-Cirrhosis and COVID-Hep[40], sizable observational cohorts such as the COVID-Cirrhosis-CHESS group[41], and population-level data, have all been used to support this. These registries were created early in the pandemic and interestingly, due to the emergence of the new Delta and Omicron variants as well as the introduction of vaccines, the relation between COVID-19 and liver will continue to evolve.

In a large registry cohort of 729 patients from 29 countries, it was discovered that mortality in individuals with cirrhosis after SARS-CoV2 infection was 32% overall, with case fatality increasing gradually with each Child-Pugh (CP) class (CLD without cirrhosis: 8%, CP-A: 19%, CP-B: 35%, CP-C: 51%)^[42]. The rates of invasive mechanical ventilation, renal replacement treatment, and intensive care unit (ICU) hospitalisation all showed similar stepwise trajectories. Additionally, after adjusting for age and comorbidities, patients with decompensated cirrhosis (CP-B and CP-C) had a considerably higher probability of dying than patients without cirrhosis who tested positive for SARS-CoV2. Reports of elevated COVID-19 mortality in cirrhosis have been confirmed in two Asian-only registries^[43] and in numerous multicenter cohort studies conducted in various geographic locations^[44-46]. Iavarone *et al* [44] observed a 30-d mortality of 30% in Northern Italy during the early stages of the pandemic, which was much greater than a historical cohort of patients with cirrhosis hospitalised with bacterial infection [44]. Decompensated cirrhosis was also reported as an independent risk factor of death in CLD patients across 21 North American institutions^[45]. Additionally, individuals with hepatocellular carcinoma (HCC) had a seven-fold higher chance of dying from COVID-19 than cirrhotic patients without HCC, indicating that this population may be particularly vulnerable to the side effects of SARS-CoV2 infection. A retrospective French cohort of > 259000 COVID-19 inpatients, including > 15000 with pre-existing CLD, showed that patients with decompensated cirrhosis had a higher adjusted risk of COVID-19 mortality^[47]. This was in contrast to the findings in a nationwide Swedish cohort, which failed to identify a connection between cirrhosis and COVID-19 related mortality^[48]. Cirrhosis overall, and decompensated cirrhosis in particular, should be considered a risk factor for death and severe COVID-19.

There are various characteristics related to the clinical course of COVID-19 in cirrhotic individuals. First, up to 46% of patients can present with acute hepatic decompensation, usually with new or worsening ascites and/or hepatic encephalopathy (HE)^[42]. This can occur between 20% and 58% of the time even in the absence of the usual COVID-19 respiratory symptoms^[42,44]. Patients with CLD present with gastrointestinal symptoms more frequently than matched controls^[42]. This is linked to a more severe disease trajectory^[45], a phenomenon that is widespread in society^[49] and is connected to increased intestinal permeability, electrolyte imbalance, and systemic inflammatory load, and is documented in up to 12% to 50%^[42-44,46] of patients with COVID-19 and decompensated cirrhosis. In the context of COVID-19, a number of well-known prognostic scoring models have been used to assess cirrhosis, with the CLIF-C ACLF score and CLIF organ failure scores surpassing Model for End-stage Liver Disease, North American Consortium for the Study of End-stage Liver Disease, and CP scores in the international and Latin American cohorts, respectively^[42,50]. Actually, the likelihood of recovery rapidly decreases as organ support requirements increase. For instance, patients with CP-C cirrhosis have a mere 21% probability of surviving if admitted to the ICU, and decreases to 10% if mechanical breathing is necessary^[42].

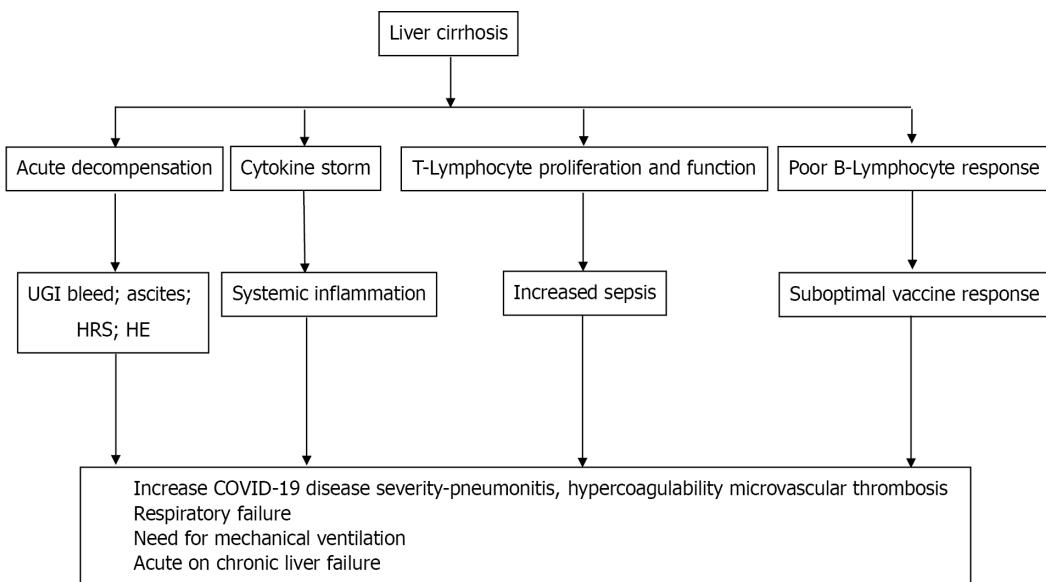
Despite the fact that SARS-CoV2 infection causes immediate hepatic decompensation, respiratory failure (71%) and problems related to the liver (19%) are the primary causes of death in individuals with cirrhosis^[42]. Hepatic dysfunction and lung damage are likely linked by a number of overlapping pathways (Figure 2), including immunological dysfunction brought on by cirrhosis, coagulopathy, and altered pulmonary dynamics due to ascites and HE^[51]. Given that the composition of the gut microbiota has been demonstrated to influence how the host immune system reacts to COVID-19, it is conceivable that intestinal permeability and dysbiosis linked to cirrhosis may also have a negative effect^[52,53].

Although COVID-19 in patients with cirrhosis is linked to a significant immediate risk of death, rates of mortality and re-admission at 90 d appear equivalent to patients with cirrhosis alone in those who survive the initial shock^[54]. Therefore, it appears that SARS-CoV2 infection does not accelerate the progression of liver disease beyond the course of cirrhosis after the acute infective period. However, up to 4 mo after recovering from acute COVID-19, hepatic MRI alterations, including enhanced T1 signaling, raised fat fraction, and hepatomegaly, have been found in 10% to 28% of otherwise healthy people^[55,56]. In both patients with and without underlying CLD, it is unknown what these radiological characteristics following COVID-19 mean clinically long-term. Furthermore, although this remains unexplored and is not considered in the current investigations, these hepatic abnormalities might not be exclusive to COVID-19 and might also be present in individuals recovering from other severe systemic insults.

It is crucial to note that studies undertaken in the years before COVID-19 vaccination and the appearance of viral variants like Delta and Omicron are largely responsible for our knowledge of the disease course in individuals with COVID-19 and cirrhosis. CLD can affect 1% to 11% of people with SARS-CoV2 infection^[57]. Numerous liver cirrhosis patients have been shown to have drunk alcohol in an ineffective effort to ward off coronavirus infection, raising the risk of alcoholic hepatitis^[58].

Implications of COVID-19 include increased mortality associated with severe COVID-19, increased risk of hepatic decompensation, and decreased routine and HCC surveillance.

Although the acute mortality associated with COVID-19 in patients with cirrhosis is substantial, the rates of death and readmission at 90 d are equivalent to those in patients with cirrhosis alone in those who survived the initial insult^[54]. Therefore, SARS-CoV2 infection does not appear to accelerate the course of liver disease beyond the typical history of cirrhosis after the acute infective period.



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Figure 2 Course of liver cirrhosis during COVID-19. UGI: Upper gastrointestinal; HRS: Hepatorenal syndrome; HE: Hepatic encephalopathy.

It is well known that infections put people at risk of decompensation (worsening ascites, encephalopathy, or acute kidney injury), and in the case of COVID-19, which is characterized by significant cytokine activation, cytokine-induced hepatocyte apoptosis and necrosis in the presence of decreased liver reserve may result in hepatic decompensation. To rule out COVID-19 as a possible cause, patients with cirrhosis who exhibit decompensation should be evaluated.

CLINICAL OUTCOMES OF PATIENTS WITH INDIVIDUAL UNDERLYING LIVER DISEASES

COVID-19 and Chronic HBV and HCV infection

As there are many etiologies (part of a systemic illness, immune mediated, direct SARS-CoV-2 infection, viral hepatitis, drug-induced, and ischemic hepatic injury) which can cause derangement of liver function tests, one of which is chronic HBV and HCV infection, it is always important to identify these underlying infections[59,60].

Prednisolone and tocilizumab have been used in the treatment of COVID-19, which are known to increase the likelihood of HBV reactivation and flare-up alongside HCV flare-up. When starting COVID-19-related therapy in those with advanced liver disease brought on by HBV and HCV, care must be taken[59,60]. Although the risk/benefit of an intervention is likely to weigh strongly when dealing with COVID-19, established criteria in such cases need to be followed to limit the risk of hepatic decompensation ([Table 1](#)).

COVID-19 and NAFLD

Risk factors in the general population for COVID-19 morbidity and mortality include advancing age, obesity, and diabetes[6]. With regard to how NAFLD affects the course of COVID-19, significant differences have been found in various studies. These differences may be attributable to problems in distinguishing the impact of NAFLD from other metabolic comorbidities due to the confounding effect of viral-induced steatosis or due to different diagnostic criteria. The latter point is especially crucial as the hepatology community at large struggles with the proposed classification modifications from NAFLD to metabolic dysfunction-associated liver disease[39]. Studies have shown that obesity is associated with increased severity and mortality in COVID-19. On the other hand, obese patients have a higher prevalence of diabetes, NAFLD, dyslipidemia, hypertension and metabolic syndrome. In a retrospective series of 202 patients with SARS-CoV2 infection, NAFLD was identified as a risk factor for progressive COVID-19, abnormal liver enzyme levels, and extended viral shedding times[61]. A study of 327 participants revealed an association between NAFLD and the likelihood of severe COVID-19 in people under 60 years of age[62]. Similar to this, MRI results from 287 SARS-CoV2 patients (79 positive, 208 negative) showed that obese patients with a concurrent liver fat fraction of less than 10% were three times more likely to develop symptoms of laboratory-confirmed COVID-19 (available as a non-peer-reviewed Preprint only)[63].

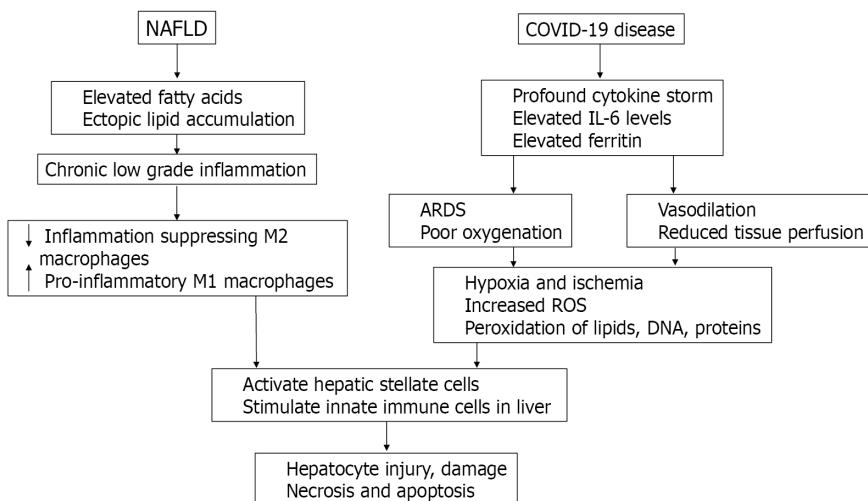
Table 1 Studies showing the effect of various etiologies of liver disease on COVID-19

Ref.	Country	Study design	Study population	Sample size	Outcome
HBV					
Anugwom et al [70], 2021	China	Letter	Peer reviewed articles with confirmed COVID-19 and HBV information	2054; HBV (<i>n</i> = 28)	Inverse relation of HBV with COVID-19
Kang et al [71], 2021	Korea	Retrospective, nationwide case-control study	Korean National Health Insurance Service COVID database	7723; HBV (<i>n</i> = 267)	Underlying chronic hepatitis B with COVID-19 severity (adjusted OR 0.65; 95%CI: 0.57-0.74)
HCV					
Richardson et al [15], 2020	United States	Case series	With confirmed COVID-19 and information on HCV infection	5700	HCV infections in < 0.1% (<i>n</i> = 3) of COVID-19 patients
Ronderos et al [72], 2021	United States	Retrospective single-center	With confirmed COVID-19 and information on HCV infection	1193; HCV (<i>n</i> = 50)	HCV infection predictor of in hospital mortality
NAFLD					
Ji et al [62], 2020	China	Retrospective	With confirmed COVID-19 and information on NAFLD status	202; NAFLD (<i>n</i> = 76)	HSI with disease progression (OR 6.4; 95%CI: 1.5-31.2)
Targher et al [64], 2020	China	Prospective observational	Laboratory confirmed COVID-19	310; NAFLD (<i>n</i> = 94)	FIB-4 (adjusted OR 1.90, 95%CI: 1.33 to 2.72) or NFS (adjusted OR 2.57, 95%CI: 1.73 to 3.82) with COVID-19 severity
Lopez-Mendez et al [65], 2021	Mexico	Retrospective	Medical records of hospitalized COVID-19	155; liver fibrosis (<i>n</i> = 69)	FIB-4 with risk of ICU admission (OR 1.74, 95%CI: 1.74-2.68; <i>P</i> = 0.023); mortality (OR 6.45, 95%CI: 2.01-20.83, <i>P</i> = 0.002)
Sachdeva et al [73], 2020	India	Systemic review	-	8142; NAFLD (<i>n</i> = 833)	Pooled adjusted 2.358 (95%CI: 1.902-2.923) with severity of COVID-19
Mahamid et al [74], 2021	Israel	Retrospective case-control	Medical records of COVID-19	71; NAFLD (<i>n</i> = 22)	OR 3.57 (95%CI: 1.22-14.48) with severity of disease
Hashemi et al [75], 2020	United States	Multicentre retrospective	Laboratory confirmed COVID-19	363; NAFLD (<i>n</i> = 55)	aOR 2.30 (95%CI: 1.27-4.17) with ICU admission
Yao et al [76], 2021	China	Retrospective	Laboratory confirmed COVID-19	86; NAFLD (<i>n</i> = 38)	OR 11.057 (95%CI: 1.193-102.439, <i>P</i> = 0.034) with severe COVID-19
Li et al [77], 2022	China and United States	Observational; 2-sample Mendelian randomization	Laboratory confirmed COVID-19	8267; NAFLD (<i>n</i> = 136)	OR 0.97 (95%CI: 0.88-1.08, <i>P</i> = 0.61) with COVID-19
BCS					
Espinosa et al [78], 2021	Brazil	Case report	Laboratory confirmed COVID-19	-	Thrombosis of an abdominal vessel should be considered as a differential diagnosis in patients with undefined abdominal pain and elevated liver biochemical tests
Sh Hassan et al [79], 2021	Saudi Arabia	Case report	Laboratory confirmed COVID-19	-	Thromboembolic events could be the first manifestation of COVID-19

COVID-19: Coronavirus disease 2019; HBV: Hepatitis B virus; HCV: Hepatitis C virus; BCS: Budd-Chiari syndrome; HSI: Hepatic steatosis index; FIB-4: Fibrosis-4; NAFLD: Non-alcoholic fatty liver disease; NFS: Non-alcoholic fatty liver disease fibrosis score; 95%CI: 95% confidence interval; OR: Odds ratio.

The chronic low-grade inflammation in NAFLD shifts macrophages from M2 to M1 phenotype and causes activation of hepatic stellate cells and the innate immune system which in collaboration with profound systemic inflammation in COVID-19 leads to hepatocyte injury, necrosis, and apoptosis (Figure 3).

Targher et al [64] reported high fibrosis-4 and NAFLD fibrosis scores with increased COVID-19 severity. Similarly, Lopez-Mendez et al [65] showed steatosis and fibrosis to be linked to increased ICU admissions. However, due to the constraints of isolation, quarantine and adequate manpower, there was a lack of detailed history and tissue histology; therefore, we do not have comparative studies of liver steatosis, steatohepatitis and fibrosis in relation to COVID-19 severity. The COVID-19 pandemic severely affected hepatology services in terms of early diagnosis, surveillance programs,



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Figure 3 Complex interplay of non-alcoholic fatty liver disease and COVID-19. COVID-19: Coronavirus disease 2019; NAFLD: Non-alcoholic fatty liver disease; ARDS: Acute respiratory distress syndrome; ROS: Reactive oxygen species; IL-6: Interleukin-6.

implementation of hepatitis B and C eradication programs, etc (Table 2).

COVID-19 and autoimmune hepatitis

Very little is known regarding the results of COVID-19 in individuals with autoimmune hepatitis (AIH), a rare form of CLD. The study by Marjot *et al*[66] in October 2020, included more than 1700 participants, and aimed to describe the course of COVID-19 and risk of unfavorable outcomes in 70 individuals with AIH. It was shown that despite the potential reporting of individuals with more severe liver disease, AIH does not significantly increase susceptibility to negative outcomes following SARS-CoV2 infection after several comparisons of non-AIH CLD and non-CLD cohorts. In contrast to the use of immunosuppressive agents, for which no adverse effects were found, age and the severity of baseline liver disease continue to be the most significant drivers of outcome in this patient group[45]. This should reassure patients and medical professionals, and support suggestions that immunosuppressive agents should not be frequently changed or stopped during COVID-19.

COVID-19 cholangiopathy

There are few case reports of secondary sclerosing cholangitis in patients with severe COVID-19 and histologic changes due to cholangiocyte injury and cholangiopathy. These patients had a protracted course and significant liver-related morbidity. Essentially, this condition was noted after recovery of COVID-19; therefore, it was called post COVID-19 cholangiopathy[67].

COVID-19 VIRAL ANTIGEN PERSISTENCE IN THE GUT

Recently, long-term sequelae of COVID-19 have been identified with symptoms of fatigue, insomnia, body ache and cognitive dysfunction. Persistence of viral antigens in gut epithelia have been documented[68]. It is possible that these persistent antigens cause immune dysfunction and low-grade persistent inflammation which manifests in various ways. It could be a basis for immune perturbation in post COVID-19. Its effect on liver in the post COVID era will be an area for research.

ADVERSE EFFECT OF mRNA VACCINES

The effects of mRNA vaccines for COVID-19 prevention have been implicated in the causation of “immune mediated hepatitis” due to the production of antibodies against the spike protein of SARS-CoV2 virus[69]. It will be interesting in the near future to detect autoimmune hepatitis or immune mediated hepatitis prevalence in the community.

Table 2 Impact of COVID-19 pandemic on hepatology services

Decrease	Increase
OPD follow-up and care	Inhospital admission
HBV treatment	Alcohol intake
HCV community level programs	HCC incidence
HCC surveillance and screening	Acute on chronic liver failure
UGI endoscopy	Gastrointestinal bleeding especially variceal bleeding
Liver transplantation	Unhealthy lifestyle
	NAFLD/MAFLD

OPD: Outpatient; COVID-19: Coronavirus disease 2019; HCC: Hepatocellular carcinoma; UGI: Upper gastrointestinal; NAFLD: Non-alcoholic fatty liver disease; MAFLD: Metabolic associated fatty liver disease.

CONCLUSION

During COVID-19, liver enzymes may be mildly elevated and generally recover without treatment. The presence of NAFLD has been linked to increased COVID-19 severity and ICU admissions. Different studies have shown the variable impact of NAFLD on COVID-19 related mortality. In patients with chronic hepatitis B and hepatitis C, a mild COVID-19 course is well tolerated, whereas in moderate-severe COVID-19 requiring steroids and/or tocilizumab, the risk of viral flare and worsening of liver disease is present. Patients with compensated cirrhosis are at increased risk of decompensation after COVID-19. In decompensated cirrhosis, the trajectory of COVID-19 severity and mortality rises with worsening Child-Pugh scores. With emerging evidence of persistent gut viral antigens capable of stimulating the immune system, we should be vigilant for postacute COVID-19 syndrome.

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FOOTNOTES

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